II. REMARKS

A. Status of the Claims

Claims 38, 47, 53, 64, and 74 were amended without prejudice or admission.

Support for "a COX-2 inhibitor and an opioid analgesic combination" in claim 38 can be found, e.g., on page 9, lines 28-30, of the specification ("[t]he invention … to the use of a pharmaceutical combination of a COX-2 inhibitor together with an opioid analgesic to provide effective management in humans.").

Support for "40 mg of oxycodone and 4 mg of nimesulide" in claims 47, 64 and 74 can be found, e.g., on page 20, lines 2-23 of the specification ("… oxycodone 40 mg plus 4 mg nimesulide …").

It is respectfully submitted that no new matter has been introduced by virtue of these amendments.

Claims 38 and 47-76 are pending and are encompassed by the elected invention, including the elected species.

B. Election/Restriction

Applicants thank the Examiner for indicating that claims 63-67, 71, 73, 75, and 76 are retained for examination in the present application.

Applicants maintain the position that the arthritic pain is not limited to pain with inflammation and includes pain without inflammation, and that claims 63-67, 71, 73, 75, and 76 read on the elected specie of pain (i.e., pain from arthritis).

C. Priority

The Office Action states that the following features of the present claims are not disclosed in the parent application (U.S. Serial No. 09/154,354) and in the provisional application (U.S. Serial No. 60/059,195):

1) an oxycodone salt in sustained release form as recited in claims 38, 54 and 64, the materials thereof as recited in claim 56, and the particle sizes recited in claims 58-59,
2) a sustained release carrier incorporated into a matrix along with oxycodone as recited in claim 61,
3) "a therapeutically effective amount of a COX-2 inhibitor together with a dose of an opioid analgesic" as recited in claim 38,
4) combinations of oxycodone to nimesulide in any therapeutically effective ratios as recited in claims 34, 54 and 63, and
5) oxycodone to nimesulide ratio of 10:1 as recited in claims 47, 64 and 74.

Applicants respectfully disagree, and submit that these features are disclosed both in the parent application and the provisional application.

With respect to the oxycodone salt in the sustained release form, the sustained release carrier incorporated into a matrix along with oxycodone, the matrix materials and the particle sizes, Applicants submit that the parent application defines the term "opioid analgesic" as "the drug in its base form, **or a pharmaceutically acceptable salt** ... thereof" (page 12, lines 19-20) (emphasis added), and includes oxycodone salts in the lists of opioid analgesics. See, e.g., page 18, lines 6-8. The parent application states, e.g., that "the opioid analgesic ... may be formulated as a controlled or sustained release oral formulation," and that "[t]he sustained release dosage form may optionally **include a sustained release carrier which is incorporated into a matrix** along with the opioid." See page 24, lines 25-30 (emphasis added). The materials recited in present claim 56 find support, e.g., on pages 33-34 of the parent application ("a matrix in addition to the opioid analgesic ... may include ... fatty acids, fatty alcohols, glyceryl esters of

fatty acids, mineral and vegetable oils and waxes ... polyalkylene glycols ... hydroxyalkylcelloses ... alkylcelluloses ... acrylic polymer and copolymers, shellac, zein ....").
The size of the particles recited in claims 58 and 59 finds support, e.g., on page 25, lines 14-17, of the parent application. The parent application therefore clearly supports the oxycodone salt in a sustained release form as recited in claims 38, 54 and 64, the sustained release carrier incorporated into a matrix along with oxycodone as recited in claim 61, the materials recited in claim 56, and the particle sizes recited in claims 58-59.

The provisional application also supports these features. The provisional application includes oxycodone salts in the definition of opioid analgesics. See, e.g., page 10. The provisional application states on page 8 that "[t]he matrix spheroid may include the sustained release carrier in the matrix itself," and that a tablet may contain "the opioid analgesic within a sustained release matrix." The materials recited in claim 56 are also recited on pages 30-34 of the provisional application. The size of the particles recited in claims 58 and 59 finds support, e.g., on page 19, lines 21-24, of the provisional application. The provisional application therefore supports the oxycodone salt in a sustained release form as recited in claims 38, 54 and 64, the sustained release carrier incorporated into a matrix along with oxycodone as recited in claim 61, the materials recited in claim 56, and the particle sizes recited in claims 58-59.

With respect to "a therapeutically effective amount of a COX-2 inhibitor together with a dose of an opioid analgesic" in claim 38, Applicants note that claim 38 has been amended without prejudice or admission to recite "a COX-2 inhibitor and an opioid analgesic combination." The Examiner has acknowledged on page 5 of the Office Action that this feature is supported, e.g., on page 15 of the provisional application.

With respect to the combinations of oxycodone to nimesulide in any therapeutically effective ratios as recited in claims 34, 54 and 63, Applicants respectfully submit that the ratio ranges recited in Table 1 of the parent application and the provisional application are the ratio ranges of the **preferred** embodiments, as, e.g., stated in the last sentence of the paragraph immediately before Table I ("In certain **preferred** embodiments, the ratio of the afore-mentioned

opioids to the afore-mentioned COX-2 inhibitors is set forth in Table I."). The provisional application states, e.g., that "[t]he present invention is related in part to the use of a COX-2 inhibitor together with an opioid analgesic," without specifying any specific ratios of the opioid analgesic to the COX-2 inhibitor. See page 6, lines 7-8. Similarly, the parent application states, e.g., that "[t]he present invention is related in part to analgesic pharmaceutical compositions comprising a COX-2 inhibitor together with an opioid analgesic," without specifying any specific ratios of the opioid analgesic to the COX-2 inhibitor. Page 6, lines 28-31. Oxycodone is included in the lists of opioid analgesics recited in the parent and the provisional applications, and nimesulide is included in the lists of COX-2 inhibitors recited in the parent and the provisional applications. Applicants therefore submit that the disclosure of the provisional application and the parent application provides ample support for the oxycodone/nimesulide combination in any therapeutically effective ratios as recited in claims 34, 54 and 63.

With respect to the oxycodone nimesulide ratio of 10:1 recited in claims 47, 64 and 74, Applicants respectfully submit that, in an effort to advance prosecution, the ratio was replaced without prejudice or admission with the "40 mg of oxycodone and 4 mg of nimesulide" ratio. The replacement ratio is literally supported, e.g., on page 20, lines 2-23, of the parent application, and on page 13, line 17, of the provisional application ("... oxycodone 40 mg plus 4 mg nimesulide ...").

An acknowledgement that the date for prior art purposes for claim 67 is September 17, 1997, the filing date of the provisional application, is respectfully requested.

D. Rejection- 35 U.S.C. § 103

Claims 38 and 47-76 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 4,569,937 to Baker et al. in view of the Swingle article and/or the Rabasseda ariticle, and further in view of U.S. Patent No. 5,472,712 to Oshlack et al. or U.S. Patent No. 6,294,195 to Oshlack et al., as evidenced by Beaver and Beaver II.

The rejection is respectfully traversed for the reasons presented in the response filed on March 8, 2010, hereby incorporated by reference, and the reasons presented below.

Independent claims 38, 54 and 63 are directed to a method of treating pain by administering nimesulide in combination with oxycodone as recited in these claims.

The cited references do not describe administration of nimesulide in combination with oxycodone, and therefore cannot teach or suggest that nimesulide is suitable for administration with oxycodone in a single dosage form as recited in claims 38, 54 and 63.

An equivalency rational therefore cannot be used to support the present rejection. See, e.g., MPEP, section 2144.06 ("[i]n order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on ... the mere fact that the components at issue are functional ... equivalents.").

Further, because the cited references do not recognize equivalency of nimesulide and NSAIDs described in the cited reference in a combination therapy with oxycodone, the combination of the cited references cannot render the present claims obvious. Id.

In addition, Applicants respectfully submit that the combination of the cited references cannot teach or suggest to the skilled person to modify the teachings of the primary reference and **combine** oxycodone with nimesulide, because Beaver I article, which has been relied by the Examiner to show that "the idea of combining NSAIDs with opioids was well established in the art at the time the presently claimed invention was made, states, e.g., that "**[u]nless** there is sufficient evidence that use of an analgesic combination is likely to yield therapeutic results unobtainable with a suitable dose of one of its constituents, **a single analgesic alone should be used**" and that "**[i]f** an optimal regimen of an NSAID alone does not provide adequate analgesia, one can add a weak opioid to the existing NSAID regimen."

In the present case, the Examiner has not indicated what in the cited references suggests that administration of the nimesulide alone will not produce adequate analgesia. Applicants respectfully submit that in the absence of this teaching, the combination of the cited reference suggests using nimesulide alone, rather than in a combination with oxycodone as recited in the present claims, and therefore cannot render claims 38, 54 and 63 obvious.

With further regard to claims 47, 64 and 74, Applicants submit that the combination of cited references does not teach or suggest administering "40 mg of oxycodone and 4 mg of nimesulide" to a human patient as recited in these claims. In response to the Examiner's calculations of the "10:1" oxycodone/nimesulide ratio on page 6 of the Office Action, Applicants respectfully submit that, unless the Examiner is able to demonstrate that a 400 mg oxycodone dose is an appropriate dose for a 10 kg child and that the 4 mg/kg rat dose in Figure 6 of the Swingle reference is directly convertible to a human dose, this comparison cannot be sustained.

With further regard to claims 70 and 75, Applicants respectfully submit that the combination of the cited references does not teach or suggest a method of treating pain in humans comprising a step of administering 4 mg of nimesulide to a human patient. In response to the Examiner's reliance on Figure 3 of the Swingle reference, Applicants again note that the doses depicted in Figure 3 of the Swingle reference are for rats, rather than human patients.

For the foregoing reasons, reconsideration and withdrawal of the rejection is respectfully requested.

E. Rejection under 35 U.S.C. § 112 (New Matter)

Claims 38 and 47-76 were rejected under 35 U.S.C. § 112, first paragraph, because, according to the Office Action, the specification does not provide support for the following features:

1) oxycodone and nimesulide in any therapeutic ratios as recited in claims 38, 54 and 64;

2) "10:1" oxycodone to nimesulide ratio recited in former claims 47, 64 and 74, and
3) an oxycodone salt in a sustained release form with materials recited in claim 56 and the particle sizes recited in claims 58-59.

The rejection is respectfully traversed.

Applicants respectfully submit that, for the reasons given above in the Priority subsection, the specification does provide ample support for (i) oxycodone and nimesulide in any therapeutic ratios as recited in claims 38, 54 and 64 and (ii) an oxycodone salt in a sustained release form with materials recited in claim 56 and the particle sizes recited in claims 58-59.

As stated above, the "10:1" oxycodone to nimesulide ratio recited in former claims 47, 64 and 74 is no longer recited in amended claims 47, 64 and 74.

Reconsideration and withdrawal of the rejection is respectfully requested.

F. Rejection under 35 U.S.C. § 112 (Indefinitness)

Claims 47, 64 and 74 were rejected under 35 U.S.C. § 112, second paragraph, for reciting the "10:1" oxycodone to nimesulide ratio.

The rejection is respectfully traversed, because the specification makes it clear that this ratio refers to the relative amounts of oxycodone and nimesulide. See, e.g., page 20, lines 16-24, of the specification.

In an effort to advance prosecution, claims 47, 64 and 74 have been amended and no longer recite the objected ratio.

Reconsideration and withdrawal of the application is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,
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